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THE CHEMOTHERAPY OF
EHRlich, WITH SPECIAL
REFERENCE TO THE
TRYPANOSOME INFECTIONS.

BY

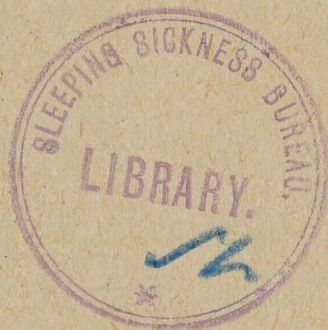
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NEW YORK

(From the Laboratories of the Rockefeller In-
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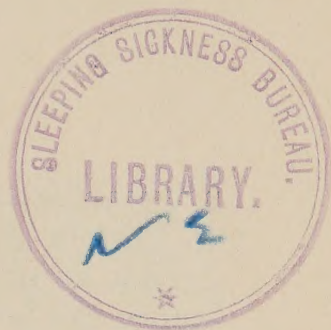
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THE CHEMOTHERAPY OF EHRLICH, WITH SPECIAL REFERENCE TO THE TRYPANOSOME INFECTIONS.*

By B. T. TERRY, M.D.,

NEW YORK.

(From the Laboratories of the Rockefeller Institute for Medical Research.)

IN his search for medicaments that might cure the trypanosome infections, Ehrlich¹ has reached two important conclusions. The first is that all chemicals which exert a curative effect on these infections are poisons. That is, they are capable, when given in sufficient quantity, of harming the vital organs of the host. In estimating the value of medicaments it is necessary, therefore, to compare the effect they have on the parasites with that they exert on the organs. The affinity the medicaments have for the parasites is termed *parasitropism*; that they have for the organs, *organotropism*.

For a medicament to have a practical value the proper relation should exist between the *organotropism* and the *parasitropism*. The *parasitropism* must be as strong as possible, and the *organotropism* as weak as possible. Under these conditions we may rid the body of the infecting parasites with the minimum of harm to the host.

*Read before the Medical Society of the County of New York, February 27, 1911.

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Fixation.—The second conception is simple, and to Ehrlich almost self-evident. It is that a parasite cannot be poisoned by a substance unless that substance can be attached or fixed to the parasite. For example, if arsenic is to injure the trypanosomes, there must be some means by which the arsenic may be attached. Should this mechanism not be present the trypanosomes could be suspended in the poisonous solution without being harmed. We shall soon see that there are solutions of arsenic in which the trypanosomes may be kept for some time without apparent harm, and others which destroy the parasites very quickly. According to Ehrlich, the difference in the action in these two cases is due to the fact that the trypanosomes have no mechanism for fixing the first solution, but have one for the second.

As a result of experiments that cannot be given here, Ehrlich believes that the fixation of various chemicals by the trypanosomes is brought about by the presence of definite chemoreceptors in the protoplasm of the parasites. These chemoreceptors have affinities for certain medicaments, and by means of these chemoreceptors the medicaments are attached to the trypanosomes.

This theory has been so productive in Ehrlich's hands that we will now apply it to results that may be obtained in the laboratory.

There are, in general, two methods of testing the value of medicaments to be employed in the treatment of trypanosome infections. The first, or *in vitro* method, is to mix the medicament directly with the trypanosomes and observe the effect upon their morphology and motility. In these experiments one must remain within certain limits of concentration, for our conception of poison is relative, and innocent substances, such as sodium chloride, have a de-

structive and killing action on living tissues if the concentration is sufficiently great. In the second, or *in vivo* method, the curative value of the medicament is tested by injecting it into an infected animal and observing the result. In order to detect a slight action that the medicament may exercise it is necessary in these tests to inject the largest non-toxic doses.

The results of these two methods of testing medicaments may or may not agree. There are four possibilities, which we shall represent as follows: O O, + +, + O, and O +.

The first possibility, or O O, is that the medicament has no action either *in vitro* or *in vivo*. This is interpreted as meaning that the parasites have no chemoreceptors for the medicament employed, or else that the substance is not a poison.

The second possibility, or + +, is that both *in vitro* and *in vivo* the medicament has a positive action on the parasites. In this case we have evidence that the mechanism for binding the medicament is present in the parasites.

The third possibility, or + O, is that the medicament *in vitro* may be active, but *in vivo* fail to influence the course of the infection. One of the most striking examples of this was found by Hata in Ehrlich's laboratory. In testing various substances upon different parasites Hata was struck by the extremely toxic action methylene blue exerted upon the spirochætæ of relapsing fever, for this substance killed the spirochætæ even in a dilution of 1 to 6,000,000. In spite of this remarkable activity the substance *in vivo* was a complete failure. Even when the dose employed was more than 500 times as large as would have been necessary to kill all of the organisms if the entire mouse had con-

sisted of nothing but spirochætæ, the curative injection into an infected mouse did not have the slightest favorable effect. This means, according to Ehrlich's theory, that the spirochætæ have chemoreceptors for the methylene blue, but that the presence of these is rendered useless by the unfavorable relation which exists between the organotropism and the parasitropism. In this particular case the organotropism is more than 500 times as strong as the parasitropism.

The fourth and last possibility, or O +, is that the medicament *in vitro* exerts no apparent effect, but *in vivo* is found to have a curative action. This is the so-called indirect, or paradoxical action, and atoxyl is a well-known example. Atoxyl in weak or strong solution exerts *in vitro* a negligible action on trypanosomes, while *in vivo*, even in dilute solution, it is highly parasitocidal. In order to explain this we may assume that the trypanosomes have no chemoreceptors for atoxyl, but that the medicament, after injection into the animal body, is converted into another for which the parasites have chemoreceptors. The possibility of this conversion occurred to Ehrlich, for he knew, from other work, that the tissues of the body exert a reducing influence. In testing his theory Ehrlich reduced atoxyl in the chemical laboratory and obtained paramidophenylarsenoxyl. Solutions of this substance he then mixed *in vitro* with trypanosomes, and found that it immobilized these parasites in less than an hour, even when the substance was diluted one million times. Ehrlich believes that the substance produced in the animal body after the introduction of atoxyl is paramidophenylarsenoxyl.

The chemical explanation for the difference in action *in vitro* of atoxyl and paramidophenylarsen-

oxyd lies in the fact that in atoxyl the arsenic rest is pentavalent, and has, therefore, no additional affinities. In paramidophenylarsenoxyd, on the other hand, the arsenic molecule is unsaturated and has a valency of three. This latter substance, therefore, possesses additional affinities, by the aid of which it is in a position to combine chemically. In other words, the arsenic receptor of the trypanosomes is adapted, not to pentavalent but to trivalent arsenic.

There is another class of substances which show the paradoxical action. If a certain pyronin is mixed *in vitro* with trypanosomes in a dilution of 1 to 20,000 or 1 to 60,000, it has, according to Ehrlich, no apparent action on the parasites. Nevertheless, if the mixture of the medicament and actively motile parasites is injected into a susceptible animal no infection takes place. In this case Ehrlich offers an entirely different explanation. In spite of the apparent lack of action, he assumes that the parasites have chemoreceptors for pyronin, and that the medicament is therefore bound to the parasites. The lack of effect *in vitro* is explained as being due to the fact that the medicament is fixed to some part of the parasite which does not influence motility or morphology. This part Ehrlich considers to be the one governing reproduction. The injected parasites have, therefore, been injured in spite of their normal appearance, and the injury consists in a sterilization. No infection followed the introduction of the parasites, for the reason that the trypanosomes were no longer able to reproduce their kind; and quickly died out after being injected.

In support of the view just given Ehrlich cites the results of Busk, who found that certain ciliates,

paramecium for example, could live for weeks in a strong solution of trypanred. Busk observed, however, that the parasites did not increase in number, and found that the sterilized action of trpanred was exerted even in very dilute solutions.

According to Ehrlich, this conception may have a very practical application. If the therapeutic dose of a sterilizing medicament is very much less than that of another which destroys the whole organism it will be possible to use very much smaller quantities of the former, and yet obtain the effect of the latter, for in an infected animal, the sterilization of all of the parasites is equivalent to killing all the organisms, when the life of the individual parasites is measured by a few hours or days. The smallness of the dose is important for the reason that all medicaments that are parasiticial are, according to Ehrlich, poisons, and the less we have to give the greater the chance of treating without doing harm to the host.

We have thus far considered normal trypanosomes. Let us now apply Ehrlich's chemoreceptor-theory to abnormal, or resistant trypanosomes, for in Ehrlich's laboratory it was found that trypanosomes could be rendered resistant to treatment, and strains of this kind have now been produced against representatives of each group of the medicaments known to be active against trypanosomes.

Resistant strains differ from the normal in that it takes more medicament *in vitro* to kill them, and, when the resistance is high, it becomes impossible to destroy the parasites in the animal body by injecting the medicament against which the resistance has been acquired. According to Ehrlich's theory, the chemoreceptors of the trypanosomes that acquire a resistance to medication have suffered a loss

of avidity for the medicament that they normally bind.

This loss of avidity of the chemoreceptors is a purely chemical conception. In the parasites there is no morphological change corresponding to it. Moreover, the loss is relative, not absolute. The diminution in the avidity is merely to the extent that the resistant trypanosomes are unable to take up the medicament in the concentration in which it is present in the body fluids of the species of animal in which the resistance was developed.

Curing Resistant Strains.—As Ehrlich had shown that resistant strains could be made in the laboratory, it was important to find some means of curing these strains, as it was quite possible that resistance might be produced unintentionally in the treatment of trypanosome infections. He therefore set himself the problem of curing animals infected with trypanosomes rendered resistant to atoxyl, and, after a number of months, found a medicament that could do this. This was arsenophenylglycin.

Ehrlich then attempted to produce a resistance to arsenophenylglycin, and again, after a certain number of months, succeeded in securing trypanosomes that could no longer be cured by this medicament.

In attempting to explain the resistance of trypanosomes to arsenophenylglycin, Ehrlich first assumed that the affinity of the arsenic receptor of the trypanosomes had undergone a further reduction. This conception, however, he soon discovered was incorrect, for, on testing *in vitro* the trypanosomes resistant to atoxyl and those resistant to arsenophenylglycin he found that it took just as much paramidophenylarsenoxyl to kill one as it did to kill the other. From this it was evident that the chemoreceptors for arsenic had not been altered.

Another explanation was, therefore, necessary, and this was soon forthcoming, for Ehrlich found a number of medicaments (derivatives of phenyl-arsenic acid) which, like arsenophenylglycin, could cure animals infected with the atoxyl resistant strain. He noted, moreover, that all of these medicaments were alike in one respect—they all contained the radical of acetic acid, $\text{CH}_2\text{CO}_2\text{H}$. He drew the conclusion, therefore, that arsenophenylglycin had acted by means of its acetyl group, and that when the strain resistant to arsenophenylglycin was produced the acetyl receptor had suffered a diminution in its avidity for the corresponding group in the medicament.

From this it would appear that trypanosomes have at least two chemoreceptors by which arsenophenylglycin may be fixed—the *acetyl* and the *arsenic* receptors. According to Ehrlich, both are active in binding the medicament. Believing that the acetyl receptor is the first to come into play, he calls this the *primary haptophore*, and the arsenic receptor the *secondary haptophore*. This process by which a medicament is bound, first by one receptor, and then by another, Ehrlich has likened to the pinning out of a butterfly, in which the first pin fixes the body, the next one wing, the next the other wing, and so on.

Aiming.—Ehrlich regards it as highly important to learn the chemoreceptors possessed by the parasites, because this knowledge can then be used to enable one to *aim* directly at the parasites we wish to destroy. For if we know all the chemoreceptors a parasite has, we can then attach corresponding side chains to some of our active radicals, *e.g.* Hg., As., or I. In this way we may force the poisonous sub-

stances on the parasites, and with deadly effect. An example will help to make this clear.

In testing various medicaments Ehrlich employed in one instance a substance that had an action on both trypanosomes and spirochætæ. He wished to increase the activity of this medicament for the spirochætæ. As iodine has a decided curative effect on syphilis, he concluded that certain spirochætæ must have iodine receptors. He therefore introduced iodine into the medicament and then tested it once more. The result showed that its destructive action for the spirochætæ had increased greatly.

The problem is, however, not at all a simple one. Although the introduction of iodine increased the value of the medicament for spirochætæ it did not leave unchanged its effectiveness against the trypanosomes, since on testing it on these organisms its activity was found to have greatly decreased. This is to be explained, according to Ehrlich, by assuming that the introduction of iodine so altered the relation of the arsenic group that the chemoreceptor for this group could not act as freely as usual. In support of this conception Ehrlich cites an example in which two chemicals unite ordinarily only at a high temperature. The introduction of a side chain into one of these chemicals so altered its relation to the other that they could combine at room temperature. The introduction of a second side chain, however, made the reaction as difficult as in the beginning, and the addition of another side chain made the union still more difficult.

Steps in Chemotherapy.—We may now give briefly the steps by which medicaments are found and improved. First of all, it is necessary to secure substances which have some action on the parasites we are trying to destroy. The attempt is then made

to determine the active groups in the medicament, and when these are known, or even before, one begins to make chemical variations in the substance with the hope of increasing its parasitropism and decreasing its organotropism. This means that we must select from our stock of chemical variations the ones which are best for therapeutic use.

Best Medicaments.—In the selection of the best medicaments several points must be borne in mind.

(1) The medicament should be *safe*. The curative dose must bear the proper relation to the lethal dose. If the former is eight or nine-tenths of the latter the medicament is too dangerous to use, unless the case is desperate and nothing better is at hand. Moreover, the medicament should not easily give rise either to resistant strains among the parasites or to hypersensitiveness in the patients.

(2) The medicament should be *efficient*. It should cure the largest possible number of species of trypanosomes, and also the largest possible number of hosts infected with these strains. It is highly desirable, furthermore, that it should be able to cure the resistant strains that are apt to have been produced by previous treatment.

(3) The medicament should be one that it is *convenient to use*. It should be easily administered, give rise to little pain, and be followed by no disagreeable or serious consequences, such as ulcers, necrosis of the skin, loss of hearing, or blindness; and

(4) The action should be *rapid* and *sure*.

When the best medicament for the treatment of laboratory animals has been found it becomes necessary to introduce it into practice. In the case of human therapy this is very difficult, for it is not possible quickly and easily to ascertain how much of

the drug a man can stand. We must begin with very small doses and gradually increase these as we find it is safe to do so. In this way we can eventually determine the maximum tolerated dose.

As a model of the way a medicament should be introduced into practice, we may take the 606 of Ehrlich and Hata. At first this medicament was entrusted only to hospitals and skilled workers, and was given free to these with the request that, in the beginning, only cases of a certain kind be treated, that careful records of the results be kept, and that these should be communicated promptly to Ehrlich. In this way the instructions which accompanied each supply of medicament that left the laboratory could be based upon the latest experimental results, and the dose could be raised as rapidly as was safe. Some twenty to thirty thousand patients were thus treated before the medicament was placed upon the market.

We may now summarize the points of most importance in introducing a medicament into human therapy. (1) *Uncomplicated* cases should be selected, in order that the action upon the disease studied may be ascertained without being obscured by the effect the drug may exercise upon some one or more of the complications. (2) *The cases chosen should not previously have been treated*, for experience has shown that the administration of one medicament may render the host hypersensitive to the influence of another. For example, it has been found that atoxyl treatment renders the host hypersensitive to acetyl-atoxyl. When sleeping sickness patients received acetyl-atoxyl after they had been treated with atoxyl, alarming symptoms appeared—symptoms that were not seen at all, or but rarely, in the treatment of patients that had not previously re-

ceived atoxyl. (3) The cases selected for treatment should be *early* ones, since experience teaches us that the later stages are much more difficult to treat. If a medicament should be judged merely by its effect upon the later stages many useful remedies would be discarded, and the opportunity of using these as a base from which to work for more effective substances would be lost.

Best Conditions.—After selecting the right patients, these should be put under the best possible conditions for observation and treatment. (1) They should be put to bed, if possible, several days before the beginning of treatment, in order that the effect of rest upon the disease may not be attributed to the medicament. (2) The diet and bowels should be regulated, and the pulse, temperature, and respiration kept under observation, and (3) Prolonged, careful records of the cases should be kept, in order that data may be at hand for determining the following points: The indications and contraindications for treatment, the dose, and the proper method of administering the drug.

The Treatment.—In general, there are two methods used in the treatment of trypanosome infections—the intermittent and the energetic. In the intermittent form a dose which is insufficient to cure the animal is administered repeatedly with intervals of a number of days between. The hope is entertained that the repetition of the small doses at these rather considerable intervals may eventually cure the animal. In the treatment of rabbits this method has given good results, but with other animals the effect has been less favorable, and in many cases bad.

By the second, or energetic method, only one treatment is given. This may consist of a single injection of the medicament, or of two large injec-

tions within forty-eight hours. When these are given the treatment is stopped, and is not again repeated if bad symptoms do not return.

Avoid the Intermittent.—In the treatment of sleeping sickness with arsenophenylglycin Ehrlich thinks that the intermittent form of treatment should be abandoned. He gives three reasons.²

(1) It is *ineffectual*. A given small dose of medicament which fails to rid the body of the parasites when first introduced is no more able to do this when repeated a number of days later.

(2) The intermittent method may lead to *hypersensitiveness* on the part of the patient, and this is doubly dangerous, since the symptoms that follow hypersensitiveness make it impracticable to increase the quantity of the medicament given, and the original dose becomes less and less effective as the tissues of the hypersensitive host bind more and more of the drug.

(3) This is the method by which *resistant strains* are produced, and resistant strains constitute one of the most serious dangers in the treatment of trypanosome infections, for they make the cure of the patient exceedingly difficult, if not impossible.

Three Groups of Medicaments.—As the result of testing perhaps thousands of preparations we have at the present time three groups of medicaments that are active against trypanosome infections. These are as follows:

(1) The arsenic and antimony group. The most important arsenic preparations are arsenious acid, atoxyl, acetyl-atoxyl, arsenophenylglycin, and, last of all, 606. Of the antimony compounds we may mention the antimonyl tartrates of potassium and sodium, aniline antimonyl tartrate, and the antimonythioglycollic acid compounds.

(2) The group of azo dyes. Examples are trypanred, trypanblue, and trypanviolet.

(3) The group of basic triphenylmethane dyes. Here we may mention parafuchsin, pyronin, and trypanosan.

Of the medicaments thus far tested the one which has given the best results in the largest number of trypanosome infections in the largest number of hosts is arsenophenylglycin. In the treatment of mice, rats, and rabbits a single dose suffices to cure. The medicament has also been of considerable value in the treatment of larger animals and of man. But its use has shown that the trypanosomes in various parts of the world react in a most variable manner. According to the way the parasites respond to treatment, Erlich divides them into three classes.

(1) The favorable case, or "*casus faustus*." Here a single dose suffices to cure, and the dose employed is only one-half or one-third of the highest tolerated dose. In the laboratory many examples of this have been met with. Ehrlich cites here the results of Strong, who, with a single injection that was only about one-half of the lethal dose, cured 90 per cent. of the monkeys (*Cynomolgus philippinensis*) infected with surra.

(2) The doubtful case, or "*casus dubius*." The medicament may cure, but the necessary dose is close to the toxic one. Medicaments which give this result may still be used to advantage in the treatment of animals that are sure to die unless treated. As an example, Ehrlich refers to the results of Strong, who found that arsenophenylglycin could save one-third to one-fifth of the horses naturally infected in the Philippines. Strong recommends, therefore, the use of arsenophenylglycin in the treatment of all valuable horses infected with surra.

(3) The unfavorable case, or "*casus infaustus*." The resistance to treatment is so great that the medicament fails altogether to cure.

The first thing to find out in practical therapy is in which of the three categories the case to be treated falls, and then to adopt the proper measures. In case two, for example, combination treatment should be resorted to. Broden is now using trypanosan in combination with arsenophenylglycin with excellent results, where arsenophenylglycin alone had proved unsatisfactory.

In Uganda, also, arsenophenylglycin has proved far from satisfactory in the treatment of sleeping sickness. The fact that many of the cases treated were very advanced may partially explain the result, but it seems practically certain that the parasites there have an unusual resistance to arsenic.

As a contrast to the result in Uganda, the experience of von Raven in Togoland should be referred to, for the sleeping sickness organisms there seem to be as easy to treat as in Uganda they are difficult. "Of twenty-three patients * * * who received two days running from 0.7 gm. to 1.2 gm. arsenophenylglycin, all were well twelve months later."³

District Treatment.—As a consequence of the remarkable variations toward the curative action of a given drug shown by trypanosomes in different regions, Ehrlich suggests that it may be necessary to adopt a form of *district treatment*. This may mean that parasites will be obtained from the regions where the usual forms of treatment are unsuccessful, taken to the laboratory, and there studied with the purpose of securing a form of treatment that shall be adapted to the infections in these particular regions.

Whether this be necessary or not will probably

depend upon the results obtained with newer medicaments, for it is always possible that some may be found which will have a wider applicability than any yet tested.

606.—The only other medicament that we shall mention is 606. This has proved to be of value, not only in the treatment of spirochetal infections, but also in those caused by the trypanosomes. After satisfactory results had been obtained in animal experiments, Ehrlich sent some of the medicament to Broden in Africa, and the latter found that an injection of 0.3 to 0.6 gm. of 606 caused the parasites to disappear promptly from his patients. The time, however, is too short for us to be able to form a judgment concerning the permanency of the result.

While it is quite possible that the best medicaments for the treatment of the trypanosomiasis have not yet been found, the situation is not at all discouraging, for the way to secure active curative agents is now known with exactness. If the medicaments in our possession prove inadequate, we have but to continue our search until the right ones are found.

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